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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,806	03/12/2002	Ben-Quan Shen	P1735R1	4225

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EXAMINER	
KAPUST, RACHEL B	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,806	SHEN ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3,5-7,9,11-13,16,17 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8,10,14,15,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, claims 1, 2, 4, 8, and 10 directed to methods of treating a NO associated disorder by administration of a VEGF variant, is acknowledged. Furthermore, Applicant's election of amino acid substitutions D63S, G65M, and L66R is acknowledged (claims 18 and 19). The traversal is on the ground(s) that Applicants argue that Groups II (claims 1, 2, 4, 8, and 10) and VIII (claims 14-19) should be rejoined because undue burden in searching would not be required. Applicant's arguments are found to be persuasive, and Groups II and VIII are rejoined.

Claims 3, 5-7, 9, 11-13, and 20 are withdrawn from further consideration by the examiner as being drawn to non-elected inventions. Claims 16 and 17 stand withdrawn from consideration as being drawn to a non-elected species. Claims 1, 2, 4, 8, 10, 14, 15, 18, and 19 are under consideration.

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/163,132, filed November 2, 1999. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a).

Information Disclosure Statement

The references cited in the Search Report received November 20, 2000 have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed within the set period for reply to this Office action.

Specification

The use of the trademarks MUTA-GENE™, NOS DETECT™, and IMAGEQUANT™ have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 8, and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating hypertension, diabetes, thrombosis, angina, atherosclerosis, and heart failure, does not reasonably provide enablement for any disorder associated with nitric oxide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants teach that nitric oxide is believed to be an important mediator of endothelial function and a regulator of vascular homeostasis, platelet aggregation, and angiogenesis (p. 4). Applicants further teach that nitric oxide is associated with hypertension, diabetes, thrombosis, angina, atherosclerosis, and heart failure (p. 11.) However, Applicants have not provided

examples of other nitric oxide associated disorders. Nitric oxide has been implicated in a number of biological functions, and often it is not clear if it has beneficial or harmful effects. For example, levels of vascular nitric oxide are decreased in hypertension, atherosclerosis, angina, and vasospasm, whereas levels of nitric oxide are increased in hypotension, sepsis, stroke, myocardial depression, and inflammatory responses (see, for example Pagliaro (2003), *Life Sci* 73(17): 2137-2149 and Marin *et al.* (1997), *Pharmacol. Ther.* 75(2): 111-134).

One of skill in the art would first need to determine whether or not nitric oxide is associated with a disorder. Then one would need to determine whether nitric oxide levels are increased or decreased in the disorder. In addition, one would need to determine whether increasing nitric oxide levels would be effective in treating the disorder. Only then would one skilled in the art be able to practice the method as taught by Applicants. Because of the lack of working examples, the breadth of the claims, and the lack of direction provided by the Applicants, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Claims 15 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VEGF variants that selectively bind KDR receptors, wherein the variants have the amino acid substitution(s) D63S, G65M, and/or L66R, does not reasonably provide enablement for any VEGF variant or VEGF variants with one or more amino acid substitutions between positions 63-66 that selectively bind KDR receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants state that VEGF variants include substitutions, deletions, and insertions, so long as the VEGF has the desired activity (p. 13, lines 17-24). Applicants further state that "VEGF" refers to the 165 amino acid protein and the related 121, 189, and 206 amino acid proteins (p. 8, lines 1-7).

The only mutations provided by Applicants are listed in Table 2. Regarding positions 63, 65, and 66, Applicants teach that residue 63 can be mutated to a serine, residue 65 can be a methionine or an alanine, and residue 66 can be an arginine or threonine. However, Applicants

have not provided any examples of other amino acid substitutions, insertions or deletions that would lead to VEGF variants that selectively bind the KDR receptor. The nucleic acid sequence and correspondingly the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which nucleotides can be deleted or inserted or substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure and function from mere sequence data are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, whereas other positions may be substituted or deleted without affecting the protein's structure/function relationship. For example, Applicants have shown that certain residues affect VEGF binding to the KDR receptor. A person of skill in the art would not know whether a VEGF variant exhibits selective binding to the KDR receptor until the gene is cloned, the protein is expressed, and binding assays are performed.

Since detailed information regarding the structural requirements of the VEGF variants is lacking, the state of the prior art, the unpredictability of the art, the lack of working examples, the breadth of the claims, and the lack of direction provided by the Applicants, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 8, 10, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Martin *et al.* (International Publication No. WO 98/20027). Claims 1, 2, 8, and 10 are drawn to methods of treating nitric oxide associated disorders by administering a VEGF receptor agonist. Martin *et al.* teach that VEGF stimulates nitric oxide production, and VEGF agonists are useful

in the treatment of nitric oxide associated conditions such as hypertension, heart failure, and atherosclerosis (p. 6, lines 4-10, p. 31, lines 11-15). Martin *et al.* further teach that VEGF may be used in the treatment of humans (p. 28, lines 14-15). Finally, Martin *et al.* teach administering VEGF proteins to the blood vessel endothelium (p. 15, lines 17-24). Thus, claims 1, 2, 8, 10, and 14 are anticipated by Martin *et al.*

Claims 1, 2, 4, 8, 10, 14, 15, and 18 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Keyt *et al.* (U.S. Patent 6,020,473). Keyt *et al.* teach VEGF variants with mutations spanning amino acids 63-67, said variants able to bind to the KDR receptor but have significantly reduced binding with respect to the FLT receptor (column 3, lines 55-61). Keyt *et al.* further teach that the VEGF variants may be used to treat surface ulcers involving the vascular endothelium such as diabetic ulcers and to treat other trauma to the vascular network (column 17, lines 43-56). Administering VEGF to a patient would inherently upregulate production of endothelial cell nitric oxide synthase (see, for example Hood *et al.* (1998), *Am. J. Phys.* 274: H1054-H1058, submitted by Applicants with IDS dated September 3, 2002). Therefore, claims 1, 2, 4, 8, 10, 14, 15, and 18 are anticipated by Keyt *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 8, 10, 14, 15, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keyt *et al.* As stated above, Keyt *et al.* teach methods of treating nitric oxide associated disorders by administering VEGF variants. More specifically, Keyt at al. teach that VEGF variants with mutations spanning amino acids 63-67 selectively bind KDR receptors. Additionally, Keyt *et al.* teach that the mutation D63A decreases VEGF binding to the FLT-1 receptor whereas wildtype-like binding to the KDR receptor was observed for D63A (column 34, line 60 through column 35, line 25). However, Keyt *et al.* do not teach the specific mutations of D63S, G65M, or L66R.

Table 1 in Keyt *et al.* lists recommended substitutions for when one wants to finely modulate the characteristics of a VEGF molecule. In Table 1, glycine and serine are both recommended substitutions for alanine. Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art to modify the variant as taught by Keyt *et al.*, D63A, by substituting serine for alanine. Motivation to do so is provided by Keyt *et al.* in that they teach creating variants that have mutations at residues 63-67 (column 3, lines 56-62, column 32, lines 41-44). One of ordinary skill in the art would have expected the modified variant to work as well as the ones exemplified .

Conclusion

NO CLAIMS ARE ALLOWED.

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

Gerber *et al.* (1998), J. Biol. Chem. 273(46): 30336-30343

U.S. Patent No. 5,851,999

U.S. Patent No. 6,057,428

U.S. Patent No. 6,475,796

U.S. Patent No. 6,239,172

U.S. Patent No. 6,485,942

U.S. Patent No. 6,395,707

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (703) 305-0634. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm. Please note for your records that as of approximately January 20, 2004, the examiner's new telephone number will be (571) 272-0886.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RBK
12/11/03

JANET ANDRES
PATENT EXAMINER